REMARKS

The amendment

Entry of the amendment is respectfully requested. No new matter is added by the amendment, as the addition of hydrogen as a possible substituent at $R^{1(i)}$, $R^{2(i)}$, $R^{3(i)}$, and $R^{4(i)}$ is supported by the application at pages 8 through 10, where each of these substituents are defined and the definition of each includes hydrogen.

The restriction requirement

Applicants elect for examination the species where: (1) the compound having vitamin PP activity or prodrug thereof is nicotinamide, a compound [*see* claim 32, for example] of formula V where b is 1, and R^{21}, R^{22}, R^{23}, R^{26}, and R^{27} are all hydrogen; and (2) the compound of formula I is N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, a compound [*see* claim 38, for example] where each of $R^{1(i)}$, $R^{2(i)}$, $R^{3(i)}$, and $R^{4(i)}$ is hydrogen, k is 0, $A^{(i)}$ is -CH=CH-, $D^{(i)}$ is $-(CH_2)_4-$, E is piperidin-4-yl, and G is 1-benzoyl.

Claims readable on the elected species are claims 32-36, 38-47, and 49.

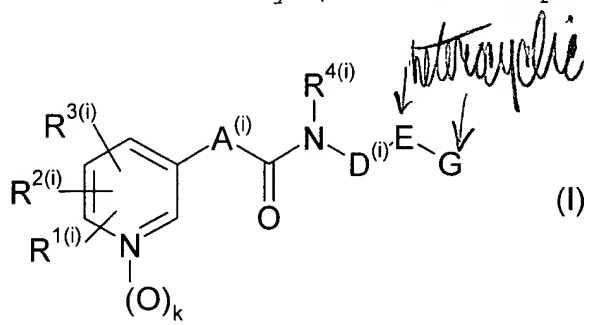
The restriction requirement is respectfully traversed. Both the compound having vitamin PP activity and the compound of formula I are defined by Markush groups, in claims 33 and 41 for the compound having vitamin PP activity, and in claims 38 and 41 for the compound of formula I.

As set forth in MPEP 803.02, second paragraph,

> Since the decisions in Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility.

The compounds having vitamin PP activity clearly share a common utility (the vitamin PP activity itself), and share a substantial common feature disclosed as being essential to that activity (all the compounds are based on 3-pyridylmethanols, 3-pyridylcarboxylates [nicotinic acids], or 3-pyridylcarboxamides [nicotinamides], and their derivatives.

The compounds of formula I also share a common activity (they are disclosed as cancerostatic or immunosuppressive agents), and share a substantial common feature disclosed as being essential to that activity (all the compounds are of the formula



(I)

as defined in claims 38 and 41.

Accordingly, Applicants submit that the restriction requirement, so phrased, is improper and should be withdrawn. Furthermore, the Examiner has made no showing of the necessity for restriction (i.e. undue burden), and the restriction requirement is improper for that reason also.

Applicants agree, however, that the Examiner may require a provisional election of a single species for examination on the merits to be given effect if the Markush claims are found not allowable, and the election made at the beginning of that section is that election.

Conclusion

Claims 32-49 are in this application, Claims 38 and 41 having been amended by this amendment. Applicants have elected a species for examination should the Markush claims not be allowable. Entry of the amendment and allowance of the claims are requested.

Respectfully submitted,

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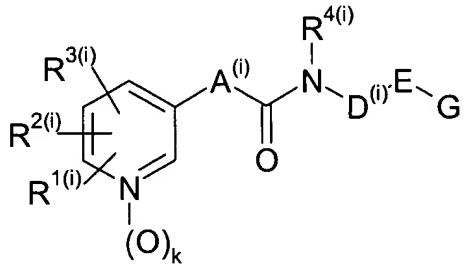
Amended claims showing amendments (additions in bold)

38. (Amended) The method of claim 32 where the cancerostatic or immunosuppressive agent is selected from the group consisting of compounds of formula I:



(I)

p.27

where:

each of $R^{1(i)}$, $R^{2(i)}$, $R^{3(i)}$, and $R^{4(i)}$ are independently selected from the group consisting of **hydrogen,** halogen, hydroxy, trifluoromethyl, cyano, aliphatic hydrocarbyl residue optionally substituted with one or more functional groups and optionally interrupted by one or more heteroatoms, and aromatic hydrocarbyl residue; or $R^{1(i)}$ and $R^{2(i)}$ together form a bridge;

k is 0 or 1;

$A^{(i)}$ and $D^{(i)}$ are independently a saturated or unsaturated optionally substituted aliphatic hydrocarbyl residue, optionally interrupted by a heteroatom or a functional group;

E is a bond or is a heterocyclic residue having one or two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen atom, linked to $D^{(i)}$ and G through a ring nitrogen atom and a ring carbon atom or through two ring nitrogen atoms; and

G is selected from the group consisting of hydrogen, an aliphatic or araliphatic residue, an unsaturated or aromatic monocyclic or polycyclic carbocyclic residue, a saturated, unsaturated, or aromatic monocyclic or polycyclic heterocyclic residue, bonded directly or through a functional group derived from a carbon, nitrogen, oxygen, sulfur, or phosphorus atom,

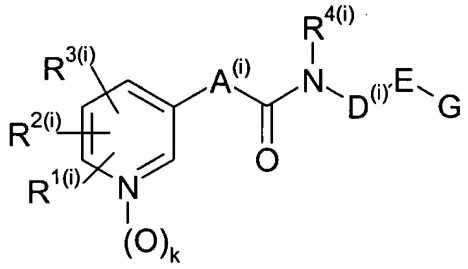
and the stereoisomers or racemic or non-racemic mixtures of stereoisomers thereof,

and the tautomers thereof when G is a heterocyclic aromatic ring or an aromatic ring substituted by a hydroxy, mercapto, or amino group,

and the pharmacologically acceptable acid addition salts thereof.

41. (Twice amended) A pharmaceutical composition comprising:

(a) at least one compound selected from the group consisting of compounds of formula I:



(I)

where:

each of $R^{1(i)}$, $R^{2(i)}$, $R^{3(i)}$, and $R^{4(i)}$ are independently selected from the group consisting of **hydrogen,** halogen, hydroxy, trifluoromethyl, cyano, aliphatic hydrocarbyl residue optionally substituted with one or more functional groups and optionally interrupted by one or more heteroatoms, and aromatic hydrocarbyl residue; or $R^{1(i)}$ and $R^{2(i)}$ together form a bridge;

k is 0 or 1;

$A^{(i)}$ and $D^{(i)}$ are independently a saturated or unsaturated optionally substituted aliphatic hydrocarbyl residue, optionally interrupted by a heteroatom or a functional group;

E is a bond or is a heterocyclic residue having one or two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen atom, linked to $D^{(i)}$ and G through a ring nitrogen atom and a ring carbon atom or through two ring nitrogen atoms; and

G is selected from the group consisting of hydrogen, an aliphatic or araliphatic residue, an unsaturated or aromatic

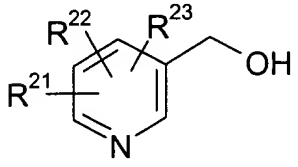
monocyclic or polycyclic carbocyclic residue, a saturated, unsaturated, or aromatic monocyclic or polycyclic heterocyclic residue, bonded directly or through a functional group derived from a carbon, nitrogen, oxygen, sulfur, or phosphorus atom,

and the stereoisomers or racemic or non-racemic mixtures of stereoisomers thereof,

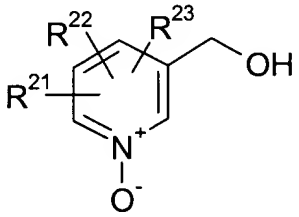
and the tautomers thereof when G is a heterocyclic aromatic ring or an aromatic ring substituted by a hydroxy, mercapto, or amino group,

and the pharmacologically acceptable acid addition salts thereof;

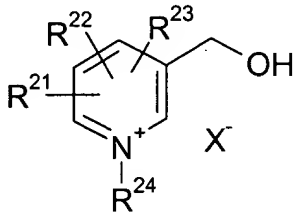
(b) at least one compound selected from the group consisting of compounds of formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb:



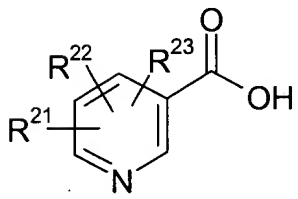
(II)



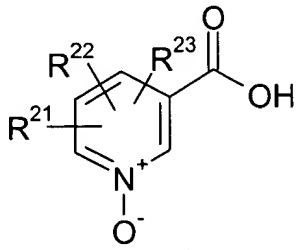
(IIa)



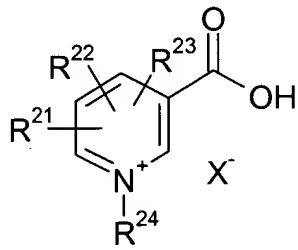
(IIb)



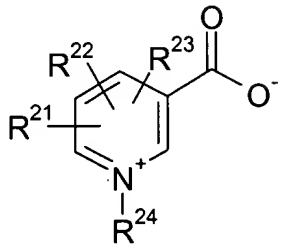
(III)



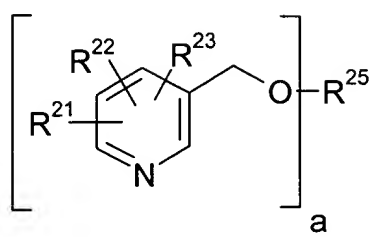
(IIIa)



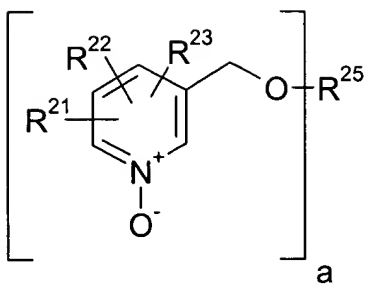
(IIIb)



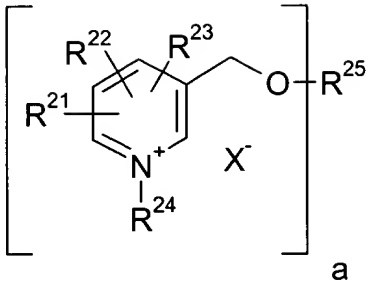
(IIIc)



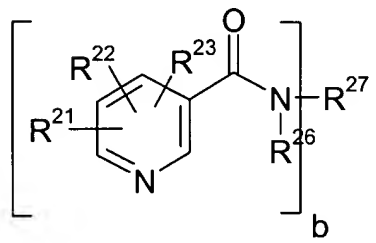
(IV)



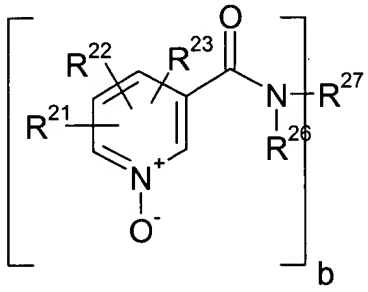
(IVa)



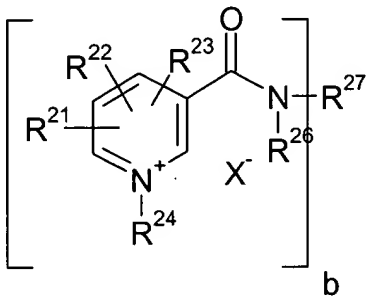
(IVb)



(V)



(Va)



(Vb)

where:

a is an integer of 1 through 6;

b is an integer of 1 through 2;

X^- is selected from the group consisting of fluoride, chloride, bromide, iodide, hydrogensulfate, mesylate, trifluoromethanesulfonate, tosylate, tetrafluoroborate, dihydrogenphosphate, and acetate;

R^{21} is selected from the group consisting of hydrogen, halogen, cyano, alkyl, trifluoromethyl, hydroxyalkyl, hydroxy, alkoxy, alkanoyloxy, alkylthio, aminoalkyl, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, and carboxy;

R^{22} is selected from the group consisting of hydrogen, halogen, alkyl, trifluoromethyl, hydroxyalkyl, hydroxy, alkoxy, alkanoyloxy, aminoalkyl, amino, alkoxycarbonyl, aminocarbonyl, and carboxy;

R^{23} is selected from the group consisting of hydrogen, alkyl, and hydroxyalkyl;

R^{24} is selected from the group consisting of alkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, and aralkyl;

R^{25} is such that the alcohol $R^{25}(OH)_a$ is selected from monovalent linear and branched C_{1-10} alkanols and ω-dialkylaminoalkanols, benzyl alcohol, divalent linear and branched C_{2-10} diols, mono- or divalent C_{5-7} cycloalkanols, C_{5-7} cycloalkanediols, C_{5-7} cycloalkanemethanols, saturated C_{5-7} heterocyclomethanols, tri-, tetra-, penta-, and hexavalent linear, branched, and cyclic alcohols with 3 to 10 carbon atoms, glycerin, 2,2-bis(hydroxymethyl)-1-octanol, erythritol, pentaerythritol, arabitol, xylitol, sorbitol, mannitol, isosorbitol, tetra(hydroxymethyl)cyclohexanol, and inositol;

R^{26} is selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, and carboxymethyl;

when b is 1, R^{27} is selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, and carboxymethyl;

when b is 2, R^{27} is alkylene in which a methylene group is optionally replaced by O, NH, or N-alkyl;

and their thioxo analogs,

and the acid addition salts or anionic salts thereof; and

(c) at least one physiologically acceptable carrier.